REMARKS

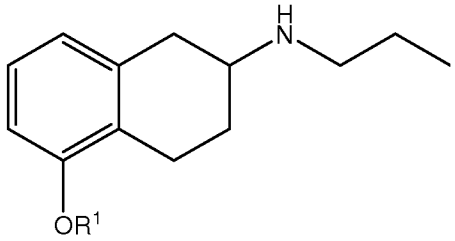
Claims 10–20 are pending in the present application, of which Claims 15–18 are presently withdrawn from consideration. Claims 1–9 and 21 were previously canceled without prejudice herein.

RESPONSE TO OFFICE ACTION DATED 2 SEPTEMBER 2009

1. Rejection Under 35 U.S.C. §103(a) Over van Vliet In View of Wikström and Rodenhuis

Claims 19–20 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over van Vliet *et al.* (1996) J. Med. Chem., 39:4233-4237 ("van Vliet") in view of Wikström *et al.* (1985) J. Med. Chem. 28:215–225 ("Wikström") and Rodenhuis (2000) Dissertation, Rijksuniversiteit Groningen titled "New, centrally acting dopaminergic agents with an improved oral bioavailability: synthesis and pharmacological evaluation" ("Rodenhuis"). This rejection is respectfully traversed.

Claim 19 is drawn to a compound having the formula



or a salt thereof, wherein the compound is in the (S)-configuration, and wherein when administered to a human body, the compound is cleaved, processed, or metabolized to (S)-2-N-propylamino-5-hydroxytetralin. For at least the reasons set forth below (Sections 1.1 and 1.2), the present Action fails to establish a presumption of *prima facie* obviousness. Further, even if a presumption of *prima facie* obviousness of Claim 19 had been established (which is not admitted herein), Applicant provides sufficient rebuttal evidence to overcome any presumption of *prima facie* obviousness (Section 1.3)

1.1. No Pattern of Preference to (1) Select Racemic 2-N-propylamino-5-hydroxytetralin, then (2) Select the (S)-Enantiomer of 2-N-propylamino-5-hydroxytetralin, then (3) Select a Prodrug of the (S)-Enantiomer

The Examiner admits that van Vliet depicts that racemic 2-N-propylamino-5-hydroxytetralin is not a highly selective D_3 receptor agonist and admits that van Vliet does "not teach the (S) enantiomer of 2-N-propylamino-5-hydroxytetralin, nor do they teach a prodrug thereof." *See* Office Action, at p. 3-4. However, the present Office Action alleges that it would have been obvious to:

(1) Select racemic 2-N-propylamino-5-hydroxytetralin from van Vliet (despite racemic 2-N-propylamino-5-hydroxytetralin having different properties than the claimed compound),

(2) Perform enantioseparation per Wikström to provide the (S)-enantiomer, and

(3) Prepare prodrugs of the (S)-enantiomer per Rodenhuis,

to arrive at the compound of Claim 19. Where is the motivation or pattern of preference to guide one of ordinary skill in the art to walk through each of steps (1)-(3)?

The Office Action (p. 3) alleges that "*van Vliet et al* teach that racemic 2-N-propylamino-5-hydroxytetralin…is a potent high-affinity D_{2L}/D_3 receptor agonist. In fact, 2-N-propylamino-5-hydroxytetralin appears to be the most potent D_{2L}/D_3 receptor agonist." However, as admitted in the Office Action (p. 3), van Vliet concludes that 26 of the 27 compounds tested, including racemic 2-N-propylamino-5-hydroxytetralin did not have a "reasonable selectivity for the D_3 receptor." See *van Vliet,* at p. 4236, col. 1, lines 5-7. At the time of the invention, D_3 selectivity was considered a promising target for the development of active agents for the treatment of different psychiatric and motor diseases. *See* the specification as filed at paragraphs **[0002]** and **[0003]**. Accordingly, one of ordinary skill in the art looking for a compound that was selective for D_3 would not have any reason to select racemic 2-N-propylamino-5-hydroxytetralin from the 27 compounds tested in van Vliet.

The art as a whole provides no motivation to select racemic 2-N-propylamino-5-hydroxytetralin. As pointed out in the present specification (paragraph **[0008]**), "the agonistic activity of [racemic 2-N-propylamino-5-hydroxytetralin] with an ED_{50} of 40 nM/kg is only moderate and the AUC and the half life are short in comparison to the other evaluated

compounds." *See* Hacksell *et al.* (1979) J. Med. Chem. 22(12):1469–1475 ("Hacksell"). It is further noted that, of 28 other compounds in Hacksell's Table I for which ED_{50} was determined, at least 8 had a lower limbic ED_{50} than 2-N-propylamino-5-hydroxytetralin; and of 20 other compounds for which AUC was determined, all but one had a higher AUC than 2-N-propylamino-5-hydroxytetralin. Swart *et al.* (1993) Toxicol. Meth. 3:279–290 (of record in the present application) describes the racemate of 2-N-propylamino-5-hydroxytetralin as a "rotigotine metabolite with weaker dopaminergic activity" and concludes that the N-dealkylated metabolites of rotigotine have a dopaminergic activity too weak for them to have therapeutic relevance. Based on the status of the art, why would one of ordinary skill in the art be motivated to select a racemic mixture that was not reasonably selective for D_3 and was predicted to have no therapeutic relevance for further testing and/or separation?

Furthermore, the secondary cited documents, Wikström and Rodenhuis, do not provide any motivation to select racemic 2-N-propylamino-5-hydroxytetralin, as neither of these documents disclose, teach or suggest racemic 2-N-propylamino-5-hydroxytetralin. Wikström and Rodenhuis thus fail to cure the deficiencies of van Vliet. The Examiner cites Wikström for allegedly teaching "enantiomeric separation of related aminotetralins to increase dopamine agonistic activity" (Office Action, p. 4). Even if, *arguendo,* this is true, this general teaching provides no motivation to select racemic 2-N-propylamino-5-hydroxytetralin. Furthermore, Wikström provides no teaching or suggestion on how to resolve the racemate to provide (S)-2-N-propylamino-5-hydroxytetralin. Similarly, Rodenhuis is cited as allegedly suggesting prodrug formulations. However, absent any motivation to select racemic 2-N-propylamino-5-hydroxytetralin, much less (S)-2-N-propylamino-5-hydroxytetralin from which to make prodrugs, Rodenhuis' general discussion of prodrug formulations does not provide guidance to one of ordinary skill in the art to arrive at the specific prodrugs of (S)-2-N-propylamino-5-hydroxytetralin in Claim 19. Accordingly, without a pattern of preference for selection of racemic 2-N-propylamino-5-hydroxytetralin, there is no pattern of preference for performing enantioseparation per Wikström to provide the (S)-enantiomer or preparing prodrugs of the (S)-enantiomer per Rodenhuis.

Clearly, such a multi-step selection (selecting racemic 2-N-propylamino-5-hydroxytetralin, performing enantioseparation to provide the (S)-enantiomer, and preparing

prodrugs of the (S)-enantiomer) can only be made in hindsight with guidance from Applicant's specification to arrive at the claimed invention. "In such circumstances, where a defendant merely throws metaphorical darts at a board filled with combinatorial prior art possibilities, courts should not succumb to hindsight claims of obviousness." *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009), emphasis added.

1.2. One of Ordinary Skill in the Art Could Not Have Predicted a Prodrug of the S-Enantiomer Would Have Successful Results

Even if, *arguendo*, motivation existed to select racemic 2-N-propylamino-5-hydroxytetralin from van Vliet for enantiomeric separation (per Wikström) and prodrug formulation (per Rodenhuis), the predictability of outcome or reasonable expectation of success required to establish a presumption of *prima facie* obviousness is lacking.

Reasonable expectation of success has long been a required criterion for a *prima facie* case of obviousness. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). In recently redefining the standards for determining obviousness, the U.S. Supreme Court in *KSR, supra* has confirmed that "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results" (emphasis added); see also MPEP 2143.01.III: "The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art" (emphasis in original).

Specifically, even if you assume, *arguendo,* that van Vliet concludes that racemic 2-N-propylamino-5-hydroxytetralin is a potent "high-affinity D_{2L}/D_3 receptor agonist", the Office Action fails to establish predictability in the:

(1) same and/or better results for (S) 2-N-propylamino-5-hydroxytetralin, and

(2) same and/or better results for prodrugs of the (S) enantiomer.

Here, in combination with van Vliet, the Examiner cites Wikström as allegedly teaching "enantiomeric separation of related aminotetralins to increase dopamine agonist activity." Specifically, the Examiner cites Wikström as having investigated the potency of "structurally and functionally related 5-hydroxy-2-(N,N-di-n-propylamino)tetralin (5-OH-DPAT)" (Office Action, p. 4). However, as articulated more fully in the past (see Office Action response dated

13 January 2009 and RCE dated 29 June 2009), the art clearly distinguishes N,N-dialkylated compounds (*i.e.* 5-OH-DPAT) from the N-dealkylated compounds (*i.e.* racemic 2-N-propylamino-5-hydroxytetralin). *See e.g.* Swart *et al.* (1993) Toxicol. Meth. 3:279–290. Therefore, one of ordinary skill in the art could not have reasonably expected to achieve the same level of success with an N-dealkylated compound, and therefore would not have applied teachings relating to a N,N-dialkylated compound (*i.e.* Wikström) to racemic 2-N-propylamino-5-hydroxytetralin for enantiomeric separation with any reasonable expectation of success.

Even if one of ordinary skill in the art would have expected one of the enantiomers to have a higher activity than the racemate, it could not have been predicted that specifically the (S)-enantiomer would exhibit the pronounced and functional D_3 selectivity shown in Table 2 of the present specification. First, the Office Action (p. 4) admits that van Vliet does not "teach the (S) enantiomer", so how could one of ordinary skill in the art predict that the (S)-enantiomer would exhibit pronounced and functional D_3 selectivity? Furthermore, the Office Action (p. 3) states that racemic 2-N-propylamino-5-hydroxytetralin is "*not* a highly selective D_3 receptor agonist" but is a potent high-affinity D_{2L}/D_3 receptor agonist. Based on racemic 2-N-propylamino-5-hydroxytetralin not being a highly selective D_3 receptor agonist, again, how could one of ordinary skill in the art predict that either enantiomer, much less the (S)-enantiomer, would exhibit pronounced and functional D_3 selectivity?

Moreover, it could not have been predicted that (S)-2-N-propylamino-5-hydroxytetralin would show purely agonistic activity. As articulated in the specification, structurally related AJ76 is described as a pure antagonist, and thus, "[t]he resulting therapeutic profile of (S)-2-N-propylamino-5-hydroxytetralin differs considerably from that of the structurally similar AJ76." *See* the specification as filed at paragraph **[0021]**. Therefore, Applicant submits that even if one of ordinary skill in the art would have been motivated to select racemic 2-N-propylamino-5-hydroxytetralin for resolution (which is not admitted herein), the fact that (1) the (S) enantiomer has pronounced and functional D3 selectivity and (2) the (S) enantiomer shows purely agonistic activity could not have been predicted by one of ordinary skill in the art. Therefore, Applicant submits, that for this additional reason, no presumption of *prima facie* case obviousness has been established.

Likewise, even if one of ordinary skill in the art would have expected improvement in oral bioavailability by formulation of prodrugs per Rodenhuis, it could not have been predicted that specifically (S)-2-N-propylamino-5-hydroxytetralin would be an attractive candidate for a prodrug search. Applicant submits that even if one of ordinary skill in the art would have been motivated to select 2-N-propylamino-5-hydroxytetralin for resolution and prodrug formulation (which is not admitted herein), no results could have been predicted – much less the positive results set forth by Applicant in the present application. Therefore, Applicant submits no presumption of *prima facie* obviousness has been established.

1.3. Rebuttal Evidence: Unexpected Results

Even if a presumption of *prima facie* obviousness of Claim 19 had been established (which is not admitted herein), the Office Action (p. 5) states "since it is unclear which competition experiments were used to measure the receptor affinity in the instant case, the results cannot be considered."

At the outset, van Vliet does not even test (S) 2-N-propylamino-5-hydroxytetralin, much less any prodrugs of the (S)-enantiomer. Therefore, any results are unexpected (whether the same or better D_3 selectivity). Furthermore, van Vliet concludes that 26 of the 27 compounds tested, including racemic 2-N-propylamino-5-hydroxytetralin, did not have a "reasonable selectivity for the D_3 receptor."

Applicant, for the first time, establishes that (S)-2-N-propylamino-5-hydroxytetralin "in fact binds with a Ki value of 7.6 nM to the D3 receptor"; and "[o]verall the receptor binding tests demonstrate a selectivity D3/D1 and D3/D5 of >1000 and ... D3/D2 of approx. 40 (Table 1)." *See* the specification as filed at paragraph **[0019]** and Table 1. Furthermore, "the structurally very similar compounds AJ76 and UH232 ... demonstrate[d] a reduced D3 preference" and AJ76 was identified as a pure antagonist, making the D3 selectivity and pure agonist activity of (S)-2-N-propylamino-5-hydroxytetralin even more unexpected. *See* specification as filed at paragraph **[0021]**.

1.4. Conclusion: 35 U.S.C. §103(a) over van Vliet in view of Wikström and Rodenhuis

Notwithstanding the comments in the Office Action specific to dependent Claim 20, Claim 20 depends from and incorporates all limitations of Claim 19 and is therefore

nonobvious for at least the same reasons that Claim 19 is nonobvious. If an independent claim is nonobvious under 35 U.S.C. §103, then any claim depending therefrom is nonobvious. MPEP 2143.03.

Withdrawal of the present rejection under 35 U.S.C. §103(a) over Hacksell in view of Wikström and Rodenhuis is respectfully requested.

2. Rejection Under 35 U.S.C. §103(a) Over van Vliet In View of Wikström and Rodenhuis, and In Further View of den Daas

Claims 10-14 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over van Vliet in view of Wikström and Rodenhuis (2000) in further view of den Daas *et al.* (1990) Naunyn-Schmiedeberg's Arch. Pharmacol. 342:655–659 ("den Daas"). This rejection is respectfully traversed.

Claim 10 is drawn to a composition containing (S)-2-N-propylamino-5-hydroxytetralin or a pharmaceutically acceptable salt or prodrug thereof and at least one pharmaceutically acceptable carrier or adjuvant. Claim 10 is rejected on similar grounds to Claim 19, with the further argument that den Daas reports "structurally and functionally related compounds" and reports that "[a]nother possibility to avoid first-pass metabolism is the administration of compounds via the transdermal route…[t]hus, noting the '[n]ext logical step in the transdermal application of dopamine agonists would be the use of transdermally applicated prodrugs'." *See* Office Action (p. 7). The Office Action (bridging p. 6-7) also asserts that den Daas reports "a pharmaceutically acceptable carrier or adjuvant, wherein the composition is adapted for transdermal, transmucosal or parenteral administration." den Daas reports "[f]or transdermal application the HCl salts were converted into the free bases and dissolved in an alcohol and polyethyleneglycol-400 mixture (6:4). All ester prodrugs proved to be stable in the solvents used for the experiments." *See* den Daas, at p. 656. Even if true (which is not admitted herein), this does not cure the deficiencies of van Vliet in view of Wikström and Rodenhuis, as it still does not provide any motivation for selecting racemic 2-N-propylamino-5-hydroxytetralin, much less the (S)-enantiomer; or provide any reasonable expectation of success that the S-enantiomer would achieve successful results.

Notwithstanding such assertion, Claim 10 is drawn to a composition comprising the

compound of Claim 19, and is therefore nonobvious for at least the same reasons that Claim 19 is nonobvious.

Claims 11-14 depend from independent Claim 10. Notwithstanding the Examiner's comments with regard to specific dependent claims, each of Claims 11-14 is nonobvious over the cited references for at least the same reasons that Claim 10 is nonobvious.

Withdrawal of the present rejection under 35 U.S.C. §103(a) over van Vliet in view of Wikström and Rodenhuis and in further view of den Daas is respectfully requested.

3. Conclusion

It is believed that all of the stated grounds of rejection are properly traversed, accommodated or rendered moot herein. Applicant therefore respectfully requests that the Examiner consider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the present Action and that the application is in condition for allowance.

Should any issues remain, the Examiner is invited to call the undersigned at the telephone number given below.